# Influenza Antiviral Medications: Summary for Clinicians

*(Current for the 2012-2013 Influenza Season)*

**Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza.**

- Influenza antiviral prescription drugs can be used to **treat** influenza or to **prevent influenza**.
- Two FDA-approved influenza antiviral medications are recommended for use in the United States during the 2012-2013 influenza season: **oseltamivir** (Tamiflu®) and **zanamivir** (Relenza®).
- Oseltamivir and zanamivir are chemically related antiviral medications known as neuraminidase inhibitors that have activity against both influenza A and B viruses.
- Antiviral resistance to oseltamivir and zanamivir among circulating influenza viruses is currently low, but this might change. Also, antiviral resistance can emerge during or after treatment in certain patients (e.g., immunosuppressed).
    - For information about antiviral drug resistance to influenza viruses and guidance on the use of influenza antiviral medications when antiviral resistance is suspected or documented this season, see Antiviral Drug-Resistance among Influenza Viruses.
    - For weekly surveillance data on antiviral resistance this season, see the FluView U.S. Influenza Surveillance Report.

## Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza

| Antiviral agent | Activity against | Use | FDA approved for | Not recommended for use in | Adverse Events |
|---|---|---|---|---|---|
| **Oseltamivir (Tamiflu®)** | **Influenza A and B** | **Treatment** | 2 wks and older | N/A | **Adverse events:** nausea, vomiting. Sporadic, transient neuropsychiatric events (self injury or delirium) mainly reported among Japanese adolescents and adults. |
| | | **Chemo-prophylaxis** | 1 yr and older | N/A | |
| **Zanamivir (Relenza®)** | **Influenza A and B** | **Treatment** | 7 yrs and older | people with underlying respiratory disease (e.g., asthma, COPD) | **Allergic reactions:** oropharyngeal or facial edema. **Adverse events:** diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections. |
| | | **Chemo-prophylaxis** | 5 yrs and older | people with underlying respiratory disease (e.g., asthma, COPD) | |

## Summary of Influenza Antiviral Treatment Recommendations

- Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and illness symptoms, and may **reduce the risk of complications from influenza** (e.g., otitis media in young children, pneumonia, respiratory failure) and death, and shorten the duration of hospitalization. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.
- Antiviral treatment is recommended **as early as possible** for any patient with confirmed or suspected influenza who
    - is hospitalized;
    - has severe, complicated, or progressive illness; or
    - is at higher risk for influenza complications.
- Persons at higher risk for influenza complications recommended for antiviral treatment include:
    - children aged younger than 2 years;*
    - adults aged 65 years and older;
    - persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
    - persons with immunosuppression, including that caused by medications or by HIV infection;
    - women who are pregnant or postpartum (within 2 weeks after delivery);
    - persons aged younger than 19 years who are receiving long-term aspirin therapy;
    - **American Indians/Alaska Natives;**
    - **persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40);** and
    - residents of nursing homes and other chronic-care facilities.
- Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for high-risk outpatients.
- When indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when started after 48 hours of illness onset, as indicated by observational studies. For example, antiviral treatment of pregnant women (of any trimester) with influenza A (2009 H1N1) virus infection has been shown to be most beneficial in preventing respiratory failure and death when started within less than 3 days of illness onset, but still provided benefit when started 3–4 days after onset compared to 5 or more days (Siston, et al JAMA 2009). A larger study reported similar findings and showed that starting oseltamivir treatment up to 4 days after illness onset provided benefit in reducing the risk of severe illness compared to later treatment of 2009 H1N1 (Yu, et al. Clinical Infectious Diseases 2011). Another study of critically ill patients and fatal

cases with 2009 H1N1 virus infection reported that antiviral treatment with a neuraminidase inhibitor was associated with improved survival compared to untreated patients, and while early treatment conveyed the most benefit, patients who started antiviral treatment up to 5 days after illness onset had improved survival compared to untreated patients (Louie, et al. Clinical Infectious Diseases 2012). A meta-analysis of observational studies of oseltamivir for treatment of influenza concluded that treatment may reduce duration of symptoms, hospitalization, and mortality compared to no treatment (Hsu, et al. 2012).

- **Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza** (see section on diagnostic testing for influenza).
- While influenza vaccination is the first and best way to prevent influenza, a history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms compatible with influenza.
- Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.†
- On December 21, 2012, the U.S. Food and Drug Administration (FDA) approved the antiviral medication oseltamivir (trade name Tamiflu®) for the treatment of influenza in people aged 2 weeks and older. An FDA press release related to this announcement is available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333205.htm.

## Diagnostic Testing for Influenza

- Rapid Influenza Diagnostic Tests (RIDTs) can be useful to identify influenza virus infection as a cause of respiratory outbreaks in any setting. RIDTs produce very quick results, but the results may not be accurate. Sensitivities of RIDTs are generally 40-70%, but a range of 10-80% has been reported compared to viral culture or reverse transcription polymerase chain reaction (RT-PCR). Specificities of RIDTs are approximately 90-95% (range 85-100%). Thus, false negative results occur more commonly than false positive results. In particular, false negative test results are common during influenza season. Clinicians should realize that a negative RIDT result does **NOT** exclude a diagnosis of influenza in a patient with suspected influenza. When there is clinical suspicion of influenza and antiviral treatment is indicated, antiviral treatment should be started as soon as possible without waiting for results of additional influenza testing.
- **Other testing** (immunofluorescence, RT-PCR, viral culture) is more accurate, but can take longer. When influenza is suspected and antiviral treatment is indicated, antiviral treatment should begin as soon as possible and should not wait for the results of testing.

## To Minimize False RIDT Results

- Collect specimens as early in the illness as possible (ideally less than 4 days from illness onset).
- Follow manufacturer's instructions, including acceptable specimens, and handling.
- Follow-up negative results with confirmatory tests (RT-PCR or viral culture) if a laboratory-confirmed influenza diagnosis is desired.

## Information on Local Influenza Activity

- Clinicians should contact their local or state health department for information about current influenza activity. For more information about influenza activity in the United States during the influenza season, visit the Weekly U.S. Influenza Surveillance Report (FluView).
- **For more information on influenza diagnostic testing**, see Clinical Description & Lab Diagnosis of Influenza.

## Recommended Dosage and Duration of Treatment or Chemoprophylaxis for Influenza Antiviral Medications

| Antiviral Agent | Use | Children | Adults |
|---|---|---|---|
| **Oseltamivir (Tamiflu®)** | **Treatment** | If younger than 1 yr old, the dose is 3 mg/kg/dose **twice** daily | 75 mg **twice** daily |
| | | **(Dose varies by child's weight)** If 1 yr or older and weigh 15 kg or less, the dose is 30 mg **twice** a day. | |
| | | If 1 yr or older and weigh more than 15 to 23 kg, the dose is 45 mg **twice** a day. | |
| | | If 1 yr or older and weigh more than 23 to 40 kg, the dose is 60 mg **twice** a day. | |
| | | If 1 yr or older and weigh more than 40 kg, the dose is 75 mg **twice** a day. | |
| | **Chemo-prophylaxis** | **(Not FDA approved for use in children younger than 1 yr old)** If child is younger than 3 months old, chemoprophylactic use is not recommended unless situation is judged critical due to limited data on use in this age group. | 75 mg **once** daily |
| | | **(Not FDA approved for children younger than 1 yr, but use in children 3 months and older and younger than 1 yr old was approved under EUA during the 2009 H1N1 pandemic)** If child 3 months or older and younger than 1 yr old, dose is 3 mg/kg/dose **once** per day. | |
| | | **(Dose varies by child's weight)** If 1 yr or older, and weigh 15 kg or less, the dose is 30 mg **once** a day. | |
| | | If 1 yr or older and weigh more than 15 to 23 kg, the dose is 45 mg **once** a day. | |
| | | If 1 yr or older and weigh more than 23 to 40 kg, the dose is 60 mg **once** a day. | |
| | | If 1 yr or older and weigh more than 40 kg, the dose is 75 mg **once** a day. | |

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| **Zanamivir (Relenza®)** | **Treatment** | 10 mg (2 inhalations) **twice** daily (**Not FDA approved for use in children younger than 7 yrs old**) | 10 mg (2 inhalations) **twice** daily |
| | **Chemo-prophylaxis** | 10 mg (2 inhalations) **once** daily (**Not FDA approved for use in children younger than 5 yrs old**) | 10 mg (2 inhalations) **once** daily |

## Duration of Treatment or Chemoprophylaxis

| | |
|---|---|
| **Treatment** | Recommended duration for antiviral treatment is 5 days. Longer treatment courses for patients who remain severely ill after 5 days of treatment can be considered. |
| **Chemo prophylaxis** | Recommended duration is 7 days after exposure. |
| | **For control of outbreaks in long-term care facilities (e.g. elderly nursing homes) and hospitals**, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks, and continuing up to 1 week after the last known case was identified. Antiviral chemoprophylaxis should be considered, especially for elderly long-term care facilities, for all exposed residents, including those who have received influenza vaccination. |

## Chemoprophylaxis:

- Annual influenza vaccination is the best way to prevent influenza because vaccination can be given well before influenza virus exposures occur, and can provide safe and effective immunity throughout the influenza season.
- Antiviral medications are approximately **70%** to **90%** effective in preventing influenza and are useful adjuncts to influenza vaccination.
- CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis so as to limit the possibilities that antiviral resistant viruses could emerge. Indiscriminate use of chemoprophylaxis might promote resistance to antiviral medications, or reduce antiviral medication availability for treatment of persons at higher risk for influenza complications or those who are severely ill.
- **An emphasis on close monitoring and early initiation of antiviral treatment is an alternative to chemoprophylaxis after a suspected exposure for some persons.**
- To be effective as chemoprophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza and continued for 7 days after the last known exposure. For persons taking antiviral chemoprophylaxis after inactivated influenza vaccination, the recommended duration is until immunity after vaccination develops (antibody development after vaccination takes about **two weeks** in adults and can take longer in children depending on age and vaccination history).
- Antiviral chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last exposure to an infectious person.

- Patients receiving antiviral chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness that might indicate influenza.

**Special Considerations for Long Term Care Facilities**

- **Chemoprophylactic use of antiviral medications to *control outbreaks among high risk persons in institutional settings* is recommended.**
- For example, when influenza is identified as a cause of respiratory outbreak among nursing home residents, use of antiviral chemoprophylaxis for all exposed or at-risk residents and for unvaccinated health care personnel is recommended. For vaccinated staff, antiviral chemoprophylaxis can be administered up to 2 weeks following influenza vaccination. For more information on the control of institutional outbreaks, please see the IDSA guidelines web site [259 KB, 30 pages].

**The following are examples of how antiviral medications can be considered for chemoprophylaxis to prevent influenza:**

- Prevention of influenza in persons at high risk of influenza complications during the first two weeks following vaccination after exposure to an infectious person.
- Prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person.
- Prevention for people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to an infectious person.
- Prevention of influenza among residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution. For more information, see IDSA guidelines web site [259 KB, 30 pages].

## Adverse Events

- When considering use of influenza antiviral medications, clinicians must consider the patient's age, weight and renal function; presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.
- For more information on safety, effectiveness and dosing for oral oseltamivir and inhaled zanamivir, visit Antiviral Drugs or consult the package inserts.

## Footnotes

* Although all children aged younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those aged younger than 2 years, with the highest hospitalization and death rates among infants aged younger than 6 months. Because many children with mild febrile respiratory illness might have other viral infections (e.g., respiratory syncytial virus, rhinovirus, parainfluenza virus, or human metapneumovirus), knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions. The likelihood of influenza virus infection in a patient depends on the prevalence of influenza activity in the local community and on the patient's signs and symptoms. Information

about influenza activity in the United States during the influenza season is available at FluView. For information on local community influenza activity, clinicians should contact their local and state health departments.

† Recommended antiviral medications (neuraminidase inhibitors) are licensed for treatment of children aged 2 weeks and older (oseltamivir) and for those aged 7 years and older (zanamivir). **However, the Advisory Committee on Immunization Practices (ACIP) and CDC recommend oseltamivir treatment of infants aged <1 year with confirmed or suspected influenza.** Oseltamivir was used for treatment of 2009 pandemic influenza A (H1N1) virus infection in children aged younger than 1 year under an Emergency Use Authorization, which expired on June 23, 2010. Limited information regarding use of oseltamivir for children from birth through age 1 year is available. Confirmation of influenza virus infection may be performed by different influenza testing methods. Information on influenza testing is available at Clinical Description & Lab Diagnosis of Influenza. In areas with limited antiviral medication availability, local public health authorities might provide additional guidance about prioritizing treatment within groups at higher risk for complications. Current CDC guidance on treatment of influenza should be consulted; updated recommendations from CDC are available on the Seasonal Influenza (Flu) site, and the ACIP antiviral recommendations [1 MB, 28 pages].

For more information, visit the Seasonal Influenza (Flu) site, or call CDC at 800-CDC-INFO (English and Spanish) or 888-232-6348 (TTY).

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